Remarks:

Claims 1-12 remain for consideration in this application with claims 1, 5, 7, 8, 9, 10, 11, and 12 being in independent format. Independent claim 1 of this application corresponds to independent claim 55 of the parent application, independent claim 5 corresponds to former independent claim 58, independent claim 7 corresponds to former independent claim 60, independent claim 8 corresponds to former independent claim 61, independent claim 9 corresponds to former independent claim 63, independent claim 10 corresponds to former independent claim 64, and independent claim 11 corresponds to former independent claim 65. Independent claim 12 is newly presented in this continuation application. These remarks address the rejections of the former claims that were contained in the Office Action of the parent case (S/N 09/573,080) and apply those same rejections to the newly added claim 12. In view of the claims as they now stand, together with the remarks hereunder, the rejections of the Office Action dated July 14, 2003 must be respectfully traversed.

All of the claims were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants agree that the "written description" requirement is severable from the "enablement" requirement. It was specifically noted in the rejection that this was not an "enablement" rejection and no such rejection appeared in the Office Action. It is asserted that the Office Action therefore contends that, while fully enabling those of skill in the art to make and use the invention commensurate in scope with the claims, there is not enough written description to show

that applicants were in possession of the invention being claimed, in this case, a genus of probes that are free of specified repeat sequences. Applicants respectfully assert that there is sufficient written description of the claimed genus in the application to overcome this rejection.

To begin, applicants note that *Vas-Cath, Inc. v. Mahurhar*, 19 USPQ2d, 1111, 1116 (Fed. Cir. 1991) provides the test for written description "[T]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" The written description requirement set forth for DNA sequences in *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) has been distinguished by the Federal Circuit in more recent cases.

> For instance, in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 ((Fed. Cir. 2002), neither the specification nor the deposited biological recited the precise "structure, formula, chemical name, or physical properties" required by *Lilly*. . . Although this court initially determined that the specification in *Enzo* did not satisfy the *Lilly* disclosure rule, it revisited the issue and remanded to the district court. The court instructed: On remand the court should determine whether a person of skill in the art would glean from the written description, including information obtainable from the deposits of the claimed sequences, subsequences, mutated variants and mixtures sufficient to demonstrate possession of the generic scope of the claims.

Moba, B.V. v. Diamond Automation, Inc., 66 USPQ2d 1429.

The Court went on to note that the Federal Circuit's most recent pronouncement clarified that "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement: rather, the requirement may be satisfied if in the knowledge of the art, the disclosed function is sufficiently correlated to a particular known

structure." *Id.*, citing, *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ 2d 1385 (Fed. Cir. 2003). As a result of the application of this standard in the Enzo and Amgen cases, "the record showed that the specification that taught one of skill in the art to make and use an invention also convinced that artisan that the inventor possessed the invention." *Id.* The same result should ensue with the present claims in this application. The claims at issue are for a genus of DNA probes that are termed "single copy." By their definition, single copy probes are found in a single location in the genome. Each one of these probes is unique and is not related structurally to any other of the single copy probes by any definable structural motif or characteristic. The combination of these unique probes into a single genus of DNA probes arises due to their similarity in their "single copy" nature and their shared function of each individually hybridizing to a single location in the genome and thereby signifying a region of single copy DNA. Finding single copy sequences is important because sequences that contain repeat sequences experience non-specific hybridization as a result of the repeat sequences hybridizing to several portions of the genome. When these repeat sequences are eliminated by only utilizing the portions between adjacent repeat sequences to make a single copy probe in accordance with the invention, the resultant single copy probes will hybridize to a single specific location in the genome which will aid in the diagnosis and treatment of chromosome abnormalities. A declaration by Dr. Joan Knoll and Dr. Peter Rogan, inventors of the present application, clarifies this utility and grouping of the probes as it would be viewed by those of skill in the relevant art.

With respect to the probes of the invention as a "genus" of probes, Applicants assert that those of skill in the art would agree that the probes fall into a single defined group of probes arranged

in terms of what chromosomal bands they hybridize to in the human genome. Such a grouping is well accepted in the art as it has been known for a long time that probes can be used to localize chromosomal abnormalities. In fact, probes have been defined in terms of which chromosomal band they occur such that probe nomenclature indicates chromosomal band location (represented in the ISCN 1995) and this is conceptually linked to the abnormalities which themselves are denoted by the chromosomal banding pattern. In many ways, these probes are similar to the FISH probes that have been used for years in the art. However, in contrast to these prior art probes, the probes of the present invention are single copy and generally smaller. Therefore, the probes of the present invention will hybridize to a single location and be useful in identifying genetic abnormalities. Many examples of the prior art probes are provided in the ISCN 1995 with one example appearing on page 97 of that reference (copies of the front page and page 97 of this reference are enclosed herein as Exhibit E). The reference is for 46, XY, inv(17)(p13q21).ish inv(17)(p13.1q21.3)(D17S379 st, RARA mv) which further defined an inverted chromosome 17 by using probes for D17S379 and RARA. In this example, the probe for locus D17S379 remained stationary (i.e. it hybridized to the proper location on chromosome 17, namely, band 17p13.1) while the RARA probe moved (i.e. the location from which it hybridized, namely band 17q21.3, and moved relative to the D17S379 probe), thereby indicating the bands which delineate the boundaries of the intrachromosomal inversion. The use of two probes in conjunction with one another helped to delineate the bands involved in the chromosomal abnormality. The same could be done with probes of the present invention although there would not be any danger of cross-hybridization due to the probe's single copy status and the precision used to localize and define the abnormalities would be greater due to the smaller probe size

and specificity. The Knoll/Rogan declaration shows that chromosomal rearrangements have been identified in every chromosomal band. Therefore, single copy FISH probes derived from all of the chromosomal bands, ie. across the entire genome, would legitimately constitute a genus of probes.

In support of the assertion that the present claims have a satisfactory written description, a declaration by Dr. Peter Rogan is provided herein. Again, it is unquestionable that the specification enables those of skill in the art how to make and use the claimed probes. It was alleged in the previous action that the specification did not contain enough examples of probes to be representative of the claimed genus of probes. To the contrary, the application fully described 9 probes from 3 different genes and enabled those of skill in the art how to find every other probe falling under the claims of the present application. Thus, the present claims are more applicable to the analysis under *Enzo* than under the *Eli Lilly* analysis which focuses on what a person of skill in the art would glean from the written description, including information obtainable from the deposits of the claimed sequences. This is because the specification clearly made use of the known sequences obtainable from the human genome drafts which were publicly available and widely used by those of skill in the art (and were also available at the time of filing this application). Thus, this "known" sequence was used to generate the useful sequences of the present application by the removal of all of the repeat sequences defined in the application as SEQ ID NOS 1-427 and 447-479 which leaves the claimed single copy sequences.

In analyzing the present claims against the accepted standard for DNA written description requirement, it is clear that the claims reasonably convey to the artisan that the inventor had possession of the claimed subject matter at the time the application was filed. The physical structure

used as a basis for all of these claims is the human genome (in part and in whole) that has been publicly disclosed through many sources including the Human Genome Project. This knowledge of the art was discussed at several locations including in the Summary of the Invention ("initial steps require knowledge of the sequences both of the target and genomic repeats, information which is increasingly available owing to the Human Genome Project and related bioinformatic studies" page 3, lines 20-23) and in the Detailed Description of the Preferred Embodiment ("a computer-based search using the term 'HIRA' was performed using Entrez Nucleotide software at the National Library of Medicine website. This identified a series of cDNA sequences for the HIRA gene in GenBank. The full length cDNA sequence was selected (GenBank Accession No. X81844), having 3859 bp. This cDNA sequence was then compared with the genome sequence which included draft sequences at the National Library of Medicine" page 19, lines 12-17). Such disclosure clearly directs those of skill in the art to the known sequences. Moreover, the process of taking these known sequences and finding the single copy sequences that are the subject matter of the present invention has already been determined to be enabled. Accordingly, the basis for the physical structure was known and disclosed in the application at the time of filing. The disclosed function of the single copy probes hybridizing to a single location is certainly "sufficiently correlated to a particular known structure", especially in light of the rule that functional limitations are acceptable limitations for what they reasonably convey to one of skill in the art (see, MPEP 2173.05(g)). The claims also include one or more of the following physical characteristics which narrow the scope of protection sought by Applicants: 1) the probe is labeled; 2) the probe has a length of at least about 2000 nucleotides; 3) the probe is free of the repeat sequences identified in the application as SEQ ID Nos. 1-428 and

447-479; 4) at least a portion of the probe is derived from either an intron or an intergenic region; and 5) the probe is complementary to a non-repetitive portion of the target.

With respect to the defining of the invention in terms of what it does not have, i.e. SEQ ID Nos. 1-428 and 447-479, such limitations are the most meaningful way to describe the instant probes. Again, these are single copy probes that each appear only once in the entire genome. These single copy probes do not contain repeat sequences as defined in the application. Specifically, the probes do not contain SEQ ID Nos. 1-427 and 447-479 and 17 mer subfragments thereof. This constitutes all repeat sequences as defined in the present application and known at the time the application was filed. The mere fact that there may be additional repeat sequences that have been discovered after the filing of this application does not make the limitation that the probes do not include the repeat sequences of SEQ ID Nos. 1-427 and 447-479 and 17 mer subfragments thereof any less definite to those of skill in the art. In fact, the continuation-in-part application (Serial No. 09/854,867) related to this application is an improvement which identifies new classes of repeat sequences and incorporates them into the database of repetitive sequences, thereby making the database of repetitive sequences more comprehensive. Moreover, that continuation-in-part application also identified approximately 65 new probes that were developed with the existing sequence database (i.e. the databases used at the time the present application was filed), thereby further supporting the contention that the databases existing at the time this application was filed were quite comprehensive. As claimed herein, the probes simply do not have any of the recited repeat sequences and contain all of the other limitations discussed above. As noted at MPEP 2173.05(I), a claim which recited the limitation "said homopolymer being free from the proteins,

soaps, resins, and sugars present in natural Nevea rubber" was considered definite because each recited limitation was definite. Having enumerated sequences, as in the present application, is certainly no less definite. Moreover, the fact that the present application provides working examples which experimentally verified that the probes of the present invention contained single copy sequences from three different chromosomal regions (selected only for their relevance to genetic diseases – not their repeat content) proves that the database of available repeat sequences at the time the application was filed must have been quite comprehensive. Accordingly, Applicants assert that the claims comply with the written description requirements for DNA sequences.

Applicants note that genetic polymorphism can produce different sequences but that these minor differences will have no impact on the probes under the conditions described in the present application and as one of skill in the art would use them. It is generally accepted by those skilled in the art that genomic sequences of different individual vary at less than 1% of the nucleotide positions. The conditions used for hybridization in the present application (which are fully enabled) allow for variation of more than 1% and hence, the hybridization results would be the same for chromosomes from different normal individuals. In fact the probes of the present invention contained DNA amplified from different individuals so the possibility exists that the enabled probes contained such polymorphism. The procedure for validating each probe involved separate hybridizations of the same probe to different normal individuals, the results of which indicated indistinguishable hybridization patterns that were consistent with individual genomes hybridized with the same probe.

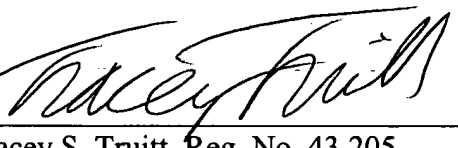
With respect to the rejection of "repeat sequence" for indefiniteness, it was alleged in Applicants' last response that such a definition is well known to those of skill in the art. In the present application, repeat sequences are defined by their sequence composition, reiteration frequency and location within a disease interval, rather than by their function. SEQ ID Nos 1-428 and 447-479 are well known to those skilled in the art as examples of repetitive sequences. Related members of the same repeat sequence families exhibit less than 100% identity among members within the same family, however a common origin of these sequences is evident based on alignments of the prototypic sequences with the sequences of genomic disease intervals. The present specification uses a minimum threshold of 60% similarity to define repeat sequence families, which is well known in the art (Jurka, J. Repeats in genomic DNA: mining and meaning. Curr. Opin. Struct. Biol. 8:333-337, 1998) (Exhibit F). This threshold is justified based on evidence that certain medium reiteration frequency repetitive sequence families in humans are ancient, originating prior to the evolution of primates. The sequence variants that distinguish members of the same repetitive sequence family have accumulated subsequent to the dispersal of various copies of these repeats throughout the genome, however, these sequences are sufficiently similar that they are commonly recognized as members of the same repeat family. In order to identify highly divergent repetitive sequence family members, it is necessary to allow for up to 40% mismatched positions when SEQ ID Nos. 1-428 and 447-479 are compared to target genomic sequences in designing probes. The parameters specifying the minimum length and genomic reiteration frequencies of repetitive sequence families in the human genome are also supported by numerous previous research studies (Li et al. Human genomic characterization of a novel locus-specific repetitive sequence. Genomics

29:397-402, 1995 (Exhibit G); Kaplan et al. Medium reiteration frequency repetitive sequences in the human genome. Nucleic Acids Res.19:4731-8, 1991. (Exhibit H)) Copies of the cited references are included with this response. These references are also useful in showing that the term "repeat sequence" is supported by the written description due to the knowledge available in the art. Page 6, lines 9-28 define repeat sequences in the present application. As is well known by those skilled in the art ". . . a repeat sequence is of sufficient length or has other qualities which would cause it to interfere with desired specific hybridization of the probe to the target DNA" (page 6, lines 17-19). When the knowledge in the art as to what constitutes a repeat sequence is combined with the teaching in the present specification, it is clear that the term "repeat sequence" is fully defined to those of skill in the art.

With respect to the referenced TATA and CAAT promoter elements and other regulatory sequences, such sequences do not meet the art definition for repeat sequences (at least 50 nucleotides in length). Furthermore, tandem repeats of TATA and CAAT of at least 50 nucleotides in length are not found in the human genome sequence draft and therefore do not meet the criterion of being present at least 10 times in the genome. With regard to the expanded triplet repeats that are known to result in genetic disorders ($(CAG)_{\geq 17}$, $(CCG)_{\geq 17}$, $(CTG)_{\geq 17}$, $(GAA)_{\geq 17}$), none are present at 10 or more positions in the human genome. For example, $CAG_{\geq 17}$ is found twice on the X chromosome and once on each of chromosomes 4, 6, 10 and 18. $GAA_{\geq 17}$ is not present in the human genome except in patients with Friedrich's Ataxia where it is expanded at a single location. Furthermore, these limitations of appearing at least 10 times in the genome and having at least 50 nucleotides each appeared in the specification of the application. Accordingly, the present application contains the

disclosure supporting the now rejected limitation, especially when considered with the knowledge of those of skill in the art and Applicants assert that this rejection should be withdrawn. In view of the foregoing, a Notice of Allowance appears to be in order and such is courteously solicited.

Respectfully submitted,

By 

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